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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/083,793	05/22/1998	BRIAN R. MURPHY	17634-000320	4558

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NATIONAL INSTITUTES OF HEALTH
OFFICE OF TECHNOLOGY TRANSFER
6011 EXECUTIVE BLVD SUITE 325
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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 11/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/083,793	MURPHY ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *144-215* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *144-215* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 May 1998* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application. This application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid. Applicant's submission filed on August 26, 2005 has been entered. Claims 144-215 are pending and under examination. The cancellation of claims 1-143 renders all previous rejections of claims 1-143 moot.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 144-165, 182-200, 214 and 215 are rejected under 35 U.S.C. 102(e) as being anticipated by Belshe *et al.* (US 5,869,036, "Belshe"). The claims are directed to isolated polynucleotide molecules comprising an operably linked:

i. Transcriptional promoter operative *in vivo* or *in vitro*,

ii. Polynucleotide sequence encoding a human PIV genome and comprising at least one sequence encoding a PIV3 *cp*45 mutation, and

iii. Transcriptional terminator operative *in vivo* or *in vitro*.

Specific PIV3 *cp*45 mutations include SEQ ID NO: 51 and 53, representing changes in the 3' leader region and the N gene start sequence, both of which are non-coding regions (Table 8), V96A, S389A, I96T, P199T, I420V, A450T, V384A, Y942H, L992F and T1558I, represented by SEQ ID NO: 55, 57, 59, 61, 63, 65, 67, 69, 71 and 73 nucleotide mutations (Table 8). Embodiments are claimed in which at least one of these mutations is present. Other embodiments require that SEQ ID NO: 51, 53, 55, 57, 59, 61, 69, 71 and 73 be present in the genome. The claims also recite that the encoded virus is capable of conferring a phenotype of attenuation of replication of at least 10-fold in the respiratory tract of a subject infected with the virus. Specifically, the L protein of the genome is a wild type protein.

Belshe contemplates the use of the hybrid viruses as immunogenic compositions (abstract). Belshe teaches hybrid *cp*45 viruses and methods of producing the viruses comprising an enveloped, negative-sense, single-stranded chimeric RNA genome, which includes, in succession from its 3'end (see Belshe's claims):

i. A nucleic acid sequence which is the same as the nucleic acid sequence of the 3' leader region of the cp45 viral genome,

ii. A nucleic acid sequence which encodes the nucleocapsid protein (NP) of cp45

iii. A nucleic acid sequence which encodes the phosphoprotein (P)

iv. A nucleic acid sequence which encodes the matrix (M) of cp45

v. A nucleic acid sequence which encodes at least one surface antigen of a target virus, and

vi. A nucleic acid sequence that encodes a variant protein that is different from the L protein of the wild-type HPIV-3.

Specific *cp*45 mutations that are contemplated by Belshe are His for Tyr at residue 942, and Phe for Leu at residue 992, represented by Applicant's SEQ ID NO: 69 and 71. Belshe's constructs use the cp45 background genome as a template for recombination. The *cp*45 genome contains all of the mutations instantly claimed (SEQ ID NO: 55, 57, 59, 61, 63, 65, 67, 69, 71 and 73). Belshe's constructs necessarily contained the complement of these mutations regardless of whether Belshe recognized *all* the mutations, see instant specification, Table 8.

As Applicant points out, a complementation assay in Example 5 demonstrates the recovery of *cp*45 hybrid virus particles. Regardless of the amount recovered, Belshe did in fact recover virus. The claims do not require a particular amount of virus be produced.

Regarding the limitation of 10-fold attenuation of replication, Applicant points to Table 11, page 102, of the specification. Table 11 discloses levels of replication in the upper and lower respiratory tract of hamsters using various constructs of wild type and mutant PIV3 viruses. Applicant's specification teaches that the majority of mutations in the L gene are responsible for the attenuated phenotype of the cp45 virus. Applicant also teaches that other mutations outside of the L gene also contribute to the cp45 attenuated phenotype. While Belshe does not demonstrate levels of attenuated replication, the hybrid viruses that Belshe describes are expected to have the property of attenuated replication of at least 10-fold. One would reasonably expect Belshe's hybrid constructs to have this characteristic because the structural features of the viruses of Belshe and the structural features of Applicant's constructs are the same as claimed. For example, Belshe's cp45 hybrid virus contains the mutation A450T in the F protein. Applicant's construct having the A450T mutation in the F protein had at least a 10-fold attenuation of replication (instant specification, Table 11).

Belshe's construct is a cp45 genome with a wild type L gene introduced. Viruses were recovered and were attenuated, thus demonstrating that the wild type L gene was not entirely responsible for attenuation (Example 5, Belshe). The cp45 genome necessarily contains mutations in genes other than the L gene, thus reading on the instant claims.

Given the disclosure of Belshe and the breadth of the instant claims, the claims are anticipated by Belshe.

Claim Rejections - 35 USC § 103

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 166-181 and 201-215 are rejected under 35 U.S.C. 103(a) as being unpatentable over Belshe. The claims are drawn to embodiments described above, wherein the genome comprises additional mutations found in the *cp*45 genome. The teachings of Belshe are summarized above. Belshe teaches the mutations of the *cp*45 genome (col. 5-6) and uses the genome as a template to insert foreign sequences (col. 9-10). The act of recombining the cp45 genome with heterologous sequences reads on the instant claims. The resulting virus contains the cp45 mutations in addition to the heterologous sequences.

Also claimed is a virus wherein the heterologous antigenic determinant comprises a transcription unit (that encodes an open reading frame) is inserted between a gene start and a gene end sequence of the PIV background genome. This limitation does not lend patentability to the claimed invention because insertion of heterologous gene encoding the antigenic determinant would only be appropriate between a gene start and gene end sequence. One would have been

motivated to use the gene start and gene end sequences of Belshe's background PIV in order to retain as much stability as possible when expressing the heterologous genes. One would have had a reasonable expectation of success given the fundamental nature of recombination and the desire to obtain stable expression. Therefore, the claimed subject matter would have been obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

4. Applicant's arguments and observations are primarily directed to the following:

- Applicant discloses that the recovery of Belshe's hybrid *cp*45 viruses was performed by a complementation assay wherein a plasmid expressing wild-type HPIV3 L protein provided a very small degree of recovery of virus plaques.
    - In response to this observation, the examiner agrees that the viruses were recovered. Regardless of the amount recovered, Belshe did recover virus (col. 8, lines 21-25). The claims do not require a particular amount of virus be produced.
- Applicant points out that Belshe's disclosure regarding hybrid *cp*45 viruses is limited to Example 7, and the mention of exchanging heterologous surface glycoproteins for those on the PIV genome.
    - In response to this observation, the specification describes a method of making the virus using the *cp*45 virus genome as a background genome into which other genes may be inserted (co. 9-10).
- Applicant points out that Belshe's explanation for attenuation is mutation of the L protein, not the wild-type. Applicant asserts that Belshe does not contemplate any

attenuated virus obtained by mutating other than the L protein. In contrast, Applicant's claims are directed to embodiments wherein the L protein is the wild-type, and the virus remains attenuated due to other temperature-sensitive mutations.

- In response to this observation, Example 5 of the Belshe patent discloses the introduction of the wild type L gene into the *cp*45 genome. Belshe recovered virus that contained a wild type L gene and also contained mutation in gene other than the L gene. Because the *cp*45 genome necessarily contains mutations in other genes besides the L gene, the introduction of the wild type L gene resulted in a virus that expressed the wild type L protein along with the other mutations that are naturally present in the *cp*45 virus (col. 8, lines 21-25).

- Applicant argues that Belshe does not disclose or suggest that any one *cp*45 mutation or all but three of the *cp*45 mutations be incorporated into the genome. Belshe does not contemplate the introduction or removal of any restriction site marker, nor that two nucleotides of a codon should be mutated to stabilize the mutation against reversion.
  - In response to these assertions, the claim language does not reflect these embodiments because the claim language is open ("comprising"). Belshe's teachings include the *cp*45 mutations, outlined in the art rejections.
- Applicant argues that Belshe does not provide the concept of inserting the heterologous gene encoding an open reading frame between the GS and GE sequences of the background PIV. This argument is particular to claims 166-178 and 201-215.
  - In response to this assertion, it would have been obvious for one of ordinary skill in the art to insert the heterologous sequence between a gene start and gene end

sequence. One would have been motivated to use the gene start and gene end sequences of Belshe's background PIV in order to retain as much stability as possible when expressing the heterologous genes. One would have had a reasonable expectation of success given the fundamental nature of recombination and the desire to obtain stable expression.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 144-215 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 53-85 of copending Application No. 09/458,813. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the copending application is a species of the instantly claimed genus of PIVs, rendering the genus claims obvious.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. Claims 144-215 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-30 and 46-74 of copending Application No. 09/459,062. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the copending application is a species of the instantly claimed genus of PIVs, rendering the genus claims obvious.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. Claims 144-215 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 84-163 of copending Application No. 09/586,479. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the copending application is a species of the instantly claimed genus of PIVs, rendering the genus claims obvious.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Claims 144-215 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 180-222 of copending Application No. 09/733,692. Although the conflicting claims are not identical, they are not patentably distinct

from each other because the subject matter of the copending application is a species of the instantly claimed genus of PIVs, rendering the genus claims obvious.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

9. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James C. Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Stacy B. Chen

Stacy B. Chen
November 10, 2005